



## Synthesis of some novel trifluoromethylated tetrahydropyrimidines using etidronic acid and evaluation for antimicrobial activity

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### Abstract

A simple and convenient, etidronic acid catalyzed, one-pot cyclocondensation reaction of 1, 3-diketone, arylaldehydes and urea to furnish trifluoromethyl tetrahydropyrimidine derivatives with excellent yield is described. The catalytic application of etidronic acid was investigated under various reaction conditions. All the synthesized compounds were evaluated for antimicrobial activity. The results obtained demonstrated that 40% of the synthesized compounds exhibited significant antimicrobial activity against all the tested micro organisms.

**Keywords:** Etidronic acid, One-pot cyclocondensation, Trifluoromethylated pyrimidines, Antimicrobial activity, Antifungal activity.

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### Introduction

Recently, there is considerable interest in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives due to their important pharmacological and therapeutic properties such as antihypertensive, antitumor, anti-inflammatory, and behaving as calcium channel blockers, a neuropeptide antagonists [1]. It is also of great interest that selective introduction of fluorine atom and fluoroalkyl functionality into heterocyclic compounds such as 1,2-dihydropyrimidines may enhance their biological and therapeutic activity [2]. However, fluoroalkyl group containing 3,4-dihydropyrimidin-2-(1*H*)-ones which may have potential therapeutic profile, are less studied [3]. These findings make it highly necessary to develop efficient methods for the synthesis of this type of pyrimidinones.

Among various approaches known for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs), three component biginelli reaction[4] is the most common. In general, Biginelli reactions are simple one pot condensation of 1,3 diketones with aldehydes and urea in the presence of catalytic amount of acid [5]. However this approach suffers low yields particularly in case of polyfunctionalized DHPMs [6]. Recently, many improved procedures have been reported using YbCl<sub>3</sub>[7], InBr<sub>3</sub>[8], InCl<sub>3</sub>[9], LiClO<sub>4</sub>[10], FeCl<sub>3</sub>•6H<sub>2</sub>O or NiCl<sub>2</sub>•6H<sub>2</sub>O[11], p-TsOH[12], LaCl<sub>3</sub>•7H<sub>2</sub>O[13], IR radiation[14], Bi(OTf)<sub>3</sub>[15], La(OTf)<sub>3</sub>[16], BF<sub>3</sub>•OEt<sub>2</sub>[17], ionic liquids (BMIm•PF<sub>6</sub> and BMIm•BF<sub>4</sub>)[18], TEBA[19], natural HEU type zeolite[20], I<sub>2</sub>[21], *N*-bromosuccinimide (NBS)[22], polyaniline–bismoclite complex[23] and other Lewis acids[24] heteropoly acid[25], sulfated alumina[26], Sr(NO<sub>3</sub>)<sub>2</sub>[27], covalently anchored sulfonic acid onto silica[28], PPE[29], and Phosphoric acid[30]. Moreover, the synthesis of fluoroalkylated tetrahydropyrimidine has been reported using ZnCl<sub>2</sub>[31] as catalyst and under microwave irradiation [32]. However, many of these reported methods also suffer from drawbacks such as cumbersome product isolation procedures, and incompatibility with other functional groups. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, still there is need for versatile, simple, and environmentally friendly processes whereby functionalized DHPMs may be formed under milder and practical conditions.

In our previous work, [33] the development of useful synthetic methodologies by employing catalysts, we found that Etidronic acid (EDA) is an efficient catalyst for the synthesis of novel pyrimidines *via* cyclocondensation. To explore further, we sought to develop new fluorine containing 3,4-dihydropyrimidin-2-(1*H*)-ones using etidronic acid as catalyst, in order to study their antimicrobial activities. Herein we report expedited synthesis of some new 3,4 DHPMs from substituted 1,3 diketone with good to excellent yields under various reaction conditions for biological interest.

## Materials and Methods

### *Experimental Section*

*General Procedures.* <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded in CDCl<sub>3</sub>, and TMS was used as an internal reference on a Bruker AVANCE II spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer. IR spectra were recorded on KBr discs, using FTIR-8400 spectrophotometer. The syntheses were carried out in a Questron Technologies Corp. QPro-M microwave synthesizer. Reactions were monitored on Merck thin layer chromatography (TLC, UV 254nm) plates. Visualization was accomplished either on UV chamber or in iodine vapor. Melting points were measured in open capillaries and are uncorrected. THF was distilled over sodium/benzophenone prior to use. Chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India) and used without purification.

### *General procedure for the preparation of tetrahydropyrimidines*

A mixture of 4,4,4-trifluoro-1-(4-methoxyphenyl) butane-1,3-dione **1** (10 mmol), different aromatic aldehydes **2a-n** (10 mmol), urea **3** (10 mmol) and etidronic acid (0.1 mmol) in dry THF were subjected to microwave irradiation at 180 W. The reactions were monitored by TLC. The

reaction mixtures were concentrated under reduced pressure and washed with water. The separated products were filtered, dried and crystallized from chloroform to furnish analytically pure products.

*4-Hydroxy-5-(4-methylbenzoyl)-6-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4a)*. White powder; mp 210-212 °C; IR (KBr):  $\nu$  3624 (-NH), 3076 (-OH), 1674 and 1660 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.27 (s, 3H, CH<sub>3</sub>), 4.16 (d, 1H, J=4.32 Hz), 5.18 (d, 1H, J=4.36 Hz), 6.86 (s, 1H, NH), 7.00 (s, 1H, NH), 7.02-7.33 (m, 9H, Ar-H), 8.22 (s, 1H, OH); MS  $m/z$ : 378(M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 60.32; H, 4.53; N, 7.40%. Found: C, 60.18; H, 4.35; N, 7.23%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-methylphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4b)*. White solid; mp 215-216 °C; IR (KBr):  $\nu$  3556 (-NH), 3290(-OH), 1672 and 1662 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$   $\delta$  2.17 (s, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 4.21 (d, 1H, J=11.04Hz), 5.02 (d, 1H, J=11.08Hz), 6.40 (s, 1H, NH), 6.71 (s, 1H, NH), 6.96-7.46 (m, 8H, Ar-H), 7.82 (s, 1H, OH); MS  $m/z$ : 392 (M<sup>+</sup>); Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 61.22; H, 4.88; N, 7.14%. Found: C, 61.05; H, 4.72; N, 6.99%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4c)*. White solid; mp 220-222 °C; IR (KBr):  $\nu$  3649 (-NH), 3292 (-OH), 1678 and 1654 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.33 (s, 3H, CH<sub>3</sub>), 3.66 (s, 3H, OCH<sub>3</sub>), 4.21 (d, 1H, J=11.0Hz), 5.01 (d, 1H, J=11.0Hz), 6.04 (s, 1H, NH), 6.47(s, 1H, NH), 6.67-7.23 (m, 6H, Ar-H), 7.43-7.47 (2H, Ar-H and 1H, OH); MS  $m/z$ : 408 (M<sup>+</sup>); Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 58.82; H, 4.69; N, 6.86%. Found: C, 58.67; H, 4.56; N, 6.71%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-chlorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4d)*. White solid; mp 198-200 °C; IR (KBr):  $\nu$  3487 (-NH), 3304 (-OH), 1688 and 1654 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.35 (s, 3H, CH<sub>3</sub>), 4.22 (d, 1H, J=10.9Hz), 5.04 (d, 1H, J=11.0Hz), 6.54 (s, 1H, NH), 6.83 (s, 1H, NH), 6.98-7.49 (m, 8H, Ar-H), 7.62 (s, 1H, OH); MS  $m/z$ : 412 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 55.28; H, 3.91; N, 6.79%. Found: C, 55.14; H, 3.79; N, 6.63%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-fluorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4e)*. White solid; mp 205-207 °C; IR (KBr):  $\nu$  3492 (-NH), 3305 (-OH), 1676 and 1662 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.28 (s, 3H, CH<sub>3</sub>), 4.24 (d, 1H, J=11.0Hz), 5.17 (d, 1H, J=10.7Hz), 6.44 (s, 1H, NH), 6.81 (s, 1H, NH), 6.91-7.61 (m, 8H, Ar-H). 7.92 (s, 1H, OH); MS  $m/z$ : 396 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>F<sub>4</sub>N<sub>2</sub>O<sub>3</sub>: C, 57.58; H, 4.07; N, 7.07%. Found: C, 57.43; H, 3.91; N, 6.92%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(3-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4f)*. Pale white powder; mp 228-230 °C; IR (KBr):  $\nu$  3463(-NH), 3096 (-OH), 1681 and 1676 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.32 (s, 3H, CH<sub>3</sub>), 4.22 (d, 1H, J=11.0Hz), 5.03 (d, 1H, J=11.03Hz), 6.06 (s, 1H, NH), 6.46 (s, 1H, NH), 6.65-7.19 (m, 8H, Ar-H). 7.72 (s, 1H, OH); MS  $m/z$ : 408 (M<sup>+</sup>); Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 58.82; H, 4.69; N, 6.86%. Found: C, 58.67; H, 4.52; N, 6.71%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(2-chlorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4g)*. White powder; mp 195-197 °C; IR (KBr):  $\nu$  3529 (-NH), 3244 (-OH), 1698 and 1669 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.33 (s, 3H, CH<sub>3</sub>), 4.22(d, 1H, J=11.0Hz), 5.01 (d, 1H, J=11.0Hz), 6.07 (s, 1H, NH), 6.47 (s, 1H, NH), 6.66-7.63 (m, 8H, Ar-H). 7.92 (s, 1H, OH); MS  $m/z$ : 412 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 55.28; H, 3.91; N, 6.79%. Found: C, 55.12; H, 3.75; N, 6.59%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4h)*. Pale yellow; mp 238-240 °C; IR (KBr):  $\nu$  3446 (-NH), 3202 (-OH), 1684 and 1672 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.35 (s, 3H, CH<sub>3</sub>), 4.28 (d, 1H, J=10.9Hz), 5.12 (d, 1H, J=11.0Hz), 6.88 (s, 1H, NH), 7.00 (s, 1H, NH), 7.25-8.35 (m, 8H, Ar-H), 8.52 (s, 1H, OH). MS  $m/z$ : 423 (M<sup>+</sup>). Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>: C, 53.91; H, 3.81; N, 9.93%. Found: C, 53.78; H, 3.68; N, 9.78%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(3-nitrophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4i)*. Solid yellow; mp 235-237 °C; IR (KBr):  $\nu$  3445 (-NH), 3218(-OH), 1710 and 1682 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.28 (s, 3H, CH<sub>3</sub>), 4.24 (d, 1H, J=10.7Hz), 5.17 (d, 1H, J=11.0Hz), 6.42 (s, 1H, NH), 6.79 (s, 1H, NH), 7.35-8.12 (m, 8H, Ar-H), 8.39 (s, 1H, OH); MS  $m/z$ : 423 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>: 53.91; H, 3.81; N, 9.93%. Found: C, 53.73; H, 3.66; N, 9.75%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(3,4-dimethoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4j)*. Solid white; mp 226-228 °C; IR (KBr):  $\nu$  3575 (-NH), 3028 (-OH), 1674 and 1652 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.33(s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 4.22 (d, 1H, J=11.0Hz), 5.05 (d, 1H, J=11.3Hz), 6.74 (s, 1H, NH), 6.89 (s, 1H, NH), 7.02-7.77 (m, 5H, Ar-H), 8.06 (2H, Ar-H and 1H, OH); MS  $m/z$ : 438 (M<sup>+</sup>); Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>: C, 57.53; H, 4.83; N, 6.39%. Found: C, 57.40; H, 4.67; N, 6.21%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(4-hydroxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4k)*. White solid; mp 228-230 °C; IR (KBr):  $\nu$  3565(-NH), 3206 (-OH), 1674 and 1666 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.36 (s, 3H, CH<sub>3</sub>), 4.22 (d, 1H, J=11.3Hz), 5.03 (d, 1H, J=11.3Hz), 6.06 (s, 1H, NH), 6.49 (s, 1H, NH), 6.65-7.39 (m, 8H, Ar-H), 7.82 (s, 1H, OH), 8.20 (s, 1H, OH); MS  $m/z$ : 394 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 57.87; H, 4.35; N, 7.10%. Found: C, 57.69; H, 4.21; N, 6.96%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(3-hydroxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4l)*. White powder; mp 215-217 °C; IR (KBr):  $\nu$  3417(-NH), 3210 (-OH), 1678 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.33 (s, 3H, CH<sub>3</sub>), 4.23 (d, 1H, J=10.9Hz), 5.03 (d, 1H, J=11.0Hz), 5.96 (s, 1H, NH), 6.39 (s, 1H, NH), 6.85-7.52 (m, 8H, Ar-H), 7.79 (s, 1H, OH), 8.06 (s, 1H, OH); MS  $m/z$ : 394 (M<sup>+</sup>); Anal. Calcd. for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 57.87; H, 4.35; N, 7.10%. Found: C, 57.74; H, 4.19; N, 6.93%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(3-bromophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4m)*. Solid white; mp 205-207 °C; IR (KBr):  $\nu$  3548 (-NH), 3092 (-OH), 1674 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$ :  $\delta$  2.27(s, 3H, CH<sub>3</sub>), 4.32 (d, 1H, J=11.0Hz), 5.18 (d, Ha, J=11.1Hz), 6.86 (s, 1H, NH), 7.01 (s, 1H, NH), 7.05-7.36 (m, 8H, ArH), 7.82 (s, 1H, OH); MS  $m/z$ : 457 (M<sup>+</sup>);

Anal. Calcd. for  $C_{19}H_{16}BrF_3N_2O_3$ : C, 49.91; H, 3.53; N, 6.13%. Found: C, 49.79; H, 3.39; N, 6.97%.

*4-Hydroxy-5-(4-methylbenzoyl)-6-(2,4-dichlorophenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (4n)*. Solid white; mp 206-208 °C; IR (KBr):  $\nu$  3613 (-NH), 3238 (-OH), 1756 (C=O)  $cm^{-1}$ ;  $^1H$  NMR:  $\delta$  2.33 (s, 3H, CH<sub>3</sub>), 4.22 (d, 1H, J=10.8Hz), 5.09 (d, 1H, J=11.0Hz), 6.06 (s, 1H, NH), 6.46 (s, 1H, NH), 6.73-7.32 (m, 7H, Ar-H), 7.56 (s, 1H, OH); MS  $m/z$ : 447 ( $M^+$ ); Anal. Calcd. for  $C_{19}H_{15}Cl_2F_3N_2O_3$ : C, 51.03; H, 3.38; N, 6.26%. Found: C, 50.88; H, 3.22; N, 6.11%.

## Results and Discussion

Etidronic acid [(1-hydroxyethylidene) bisphosphonic acid] is one of the bisphosphonic acid derivative and also known as bisphosphonate having molecular formula  $C_2H_8O_7P_2$ . The two  $PO_3$  (phosphonate) groups covalently linked to carbon atom [34] (Figure 1). EDA is mild enough as compare to another strong acid did not affect acid sensitive aldehydes.

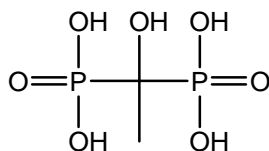
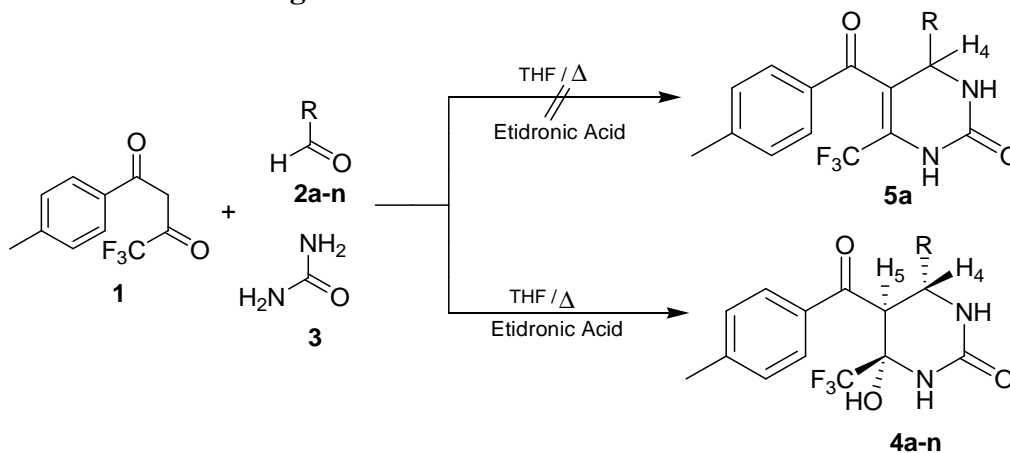


Figure 1. Structure of Etidronic Acid



### Scheme 1 Synthesis of trifluoromethyl substituted tetrahydropyrimidines using Etidronic acid as a catalyst

Initially, condensation of the 4,4,4-trifluoro-1-(4-methylphenyl) butane-1,3-dione (**1**) with benzaldehyde (**2a**) and urea (**3**) took place smoothly in the presence of EDA in THF to result in the formation of trifluoromethyl tetrahydropyrimidine **4a** in 89% yield (entry 1, table 1). Thus we found that the final product obtained was tetrahydropyrimidines

**Table 1. Optimization of the reaction conditions for the synthesis of 4a.**

Entry <sup>a</sup>	Catalyst (equiv)	Solvent	Yield <sup>b</sup> %	Time min
1	EDA (1.0)	THF	95	3.5
2	EDA (0.1)	THF	93	4.0
3	EDA (0.1)	MeOH	82	6.5
4	EDA (0.1)	EtOH	86	5.5
5	EDA (0.1)	Dioxane	79	4.5

<sup>a</sup>The reactions were conducted under microwave irradiation (180 W). <sup>b</sup>Isolated yield after purification.

instead of usual dihydro biginelli product **5a**. A similar observation was made by Bose et al[19] during TEBA catalyzed Biginelli condensation. The condensation of **1** with **2a** and **3** to generate **4a** was investigated under a variety of conditions and the results are summarized in table 1. The condensation reaction with a catalytic amount of EDA was cleaned in THF, it took a longer time (entry 2, Table 1). On the other hand, the reaction was relatively fast when one equiv. of EDA was employed (entry 1, Table 1). The yield of desired product **4a** was moderate when methanol, ethanol and dioxane were used (entry 3-5, Table 1). In case of methanol and ethanol, the product **4a** was separated by column chromatography over silica gel using hexane/EtOAc (7:3) as eluent. Thus, it is clear from the aforementioned experiments that the best yield of compound **4a** could be obtained by employing catalytic amount of etidronic acid in THF under microwave irradiation.

**Table 2. Synthesis of Trifluoromethyl Functionalized Tetrahydropyrimidines using etidronic acid (catalyst) and THF under microwave irradiation**

Entry	R	Products	Yield <sup>a</sup> (%)	Time/min.
1	Ph	<b>4a</b>	93	4.0
2	4-CH <sub>3</sub> Ph	<b>4b</b>	91	4.5
3	4-OCH <sub>3</sub> Ph	<b>4c</b>	90	3.5
4	4-ClPh	<b>4d</b>	89	4.3
5	4-FPh	<b>4e</b>	90	4.5
6	3-OCH <sub>3</sub> Ph	<b>4f</b>	92	3.5
7	2-ClPh	<b>4g</b>	86	4.5
8	4-NO <sub>2</sub> Ph	<b>4h</b>	91	3.0
9	3-NO <sub>2</sub> Ph	<b>4i</b>	89	3.5
10	3,4-diOCH <sub>3</sub> Ph	<b>4j</b>	92	4.5
11	4-OHPh	<b>4k</b>	87	5.0
12	3-OHPh	<b>4l</b>	88	4.5
13	3-BrPh	<b>4m</b>	86	4.0
14	2,4-diClPh	<b>4n</b>	89	3.5

<sup>a</sup>Isolated yields after purification.

It was also found that the electron deficiency and nature of the substituents on the aromatic ring aldehydes (**2a-n**) affect the conversion rate; aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 3, entries 8, 9) reacted faster than electron-donating groups

(Table 2, entries 3,5,11). All the synthesized compounds were characterized by spectroscopy analysis and confirmed by the earlier reports [19, 32]. In MS spectrum of **4b** molecular ion peak appears at 392 m/z which reveals that formation of tetrahydropyrimidine. The <sup>1</sup>H NMR spectrum of **4b** displayed two characteristic doublets for the *trans*-axial methane protons at 4.18-4.21 and 4.99-5.02  $\delta$ . The observed coupling constant  $J = 11.04$  Hz and 11.08 Hz assigned to the H<sub>4</sub> and H<sub>5</sub> protons, respectively. The overall study indicates that etidronic acid was an efficient catalyst for the synthesis fluoroalkylated dihydropyrimidines in excellent yields.

**Table 3. Antimicrobial activity of trifluoromethylated pyrimidine derivatives 4a-n**

Compounds	Zone of inhibition in mm <sup>a</sup>				Zone of inhibition in mm <sup>b</sup>
	<i>E.coli</i>	<i>P.vulgaris</i>	<i>B.mega</i>	<i>S.sureus</i>	<i>A.niger</i>
<b>4a</b>	17	22	12	13	15
<b>4b</b>	15	20	22	13	15
<b>4c</b>	16	16	13	11	14
<b>4d</b>	16	15	21	21	16
<b>4e</b>	20	17	18	22	15
<b>4f</b>	13	15	19	17	15
<b>4g</b>	13	14	21	19	22
<b>4h</b>	17	14	15	20	21
<b>4i</b>	18	14	15	11	20
<b>4j</b>	21	21	19	23	12
<b>4k</b>	23	12	18	14	23
<b>4l</b>	22	18	12	24	18
<b>4m</b>	19	18	21	12	20
<b>4n</b>	17	18	16	17	12
<b>S1</b>	25	20	20	24	-
<b>S2</b>	27	21	25	25	-
<b>S3</b>	24	25	23	24	-
<b>S4</b>	21	20	25	23	-
<b>S5</b>	-	-	-	-	25

<sup>a</sup>Antibacterial activity, <sup>b</sup>Antifungal activity; **S1** = Amoxicillin, **S2** = Ampicillin, **S3** = Ciprofloxacin, **S4** = Erythromycin, **S5** = Griseofulvin.

All the synthesized compounds were evaluated for antimicrobial activity against four different strains (two gram +ve viz. *S. aureus* and *B.mega* and two gram -ve viz. *E. coli* and *P. vulgaris*) by cup-plate [35] method. Among all the compounds, compounds **4a**, **4b** and **4l** were demonstrated good activity against *P.Vulgaris*, *B. Mega* and *E.Coli*, respectively. While compounds **4j** and **4k** were exhibited promising activity against *E.Coli* and *P.Vulgaris*. Moreover, Compound **4k** was exhibit good antifungal activity against *A.Niger*. The results were compared with standard antibiotics like Amoxicillin, Ampicillin, Ciprofloxacin, Erythromycin and Griseofulvin. Inhibition was recorded by measuring the diameter of the inhibition zone. Each experiment was repeated twice and the average of the two independent determinations was recorded. The results are cited in table 3.

## Conclusion

In summary, we have demonstrated a simple route for the synthesis of trifluoromethylated tetrahydropyrimidines using etidronic acid and evaluated for antimicrobial activity. Some of the newly synthesized compounds were exhibited well to excellent activity against both gram positive and gram negative bacteria and fungi. This scheme was general and provides fluoroalkylated pyrimidines in moderate to excellent yields depending on the reactivity of arylaldehydes. The cyclocondensation reaction works well with a catalytic amount of etidronic acid. Thus, the present synthesis of pyrimidines will serve as an exclusive method of preparative importance for this class of compounds. We are currently engaged in the application of this catalyst for the electrophilic reaction.

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